

HIGHLIGHT set on as ''
? b 155 434 55
 21oct99 10:08:53 User231882 Session D471.2
 \$0.00 0.050 DialUnits File410
 \$0.00 Estimated cost File410
 \$0.06 TYMNET
 \$0.06 Estimated cost this search
 \$0.08 Estimated total session cost 0.201 DialUnits

SYSTEM:OS - DIALOG OneSearch
File 155: MEDLINE(R) 1966-1999/Dec W2
 (c) format only 1999 Dialog Corporation
*File 155: reloaded, note accession numbers changed.
File 434: SciSearch(R) Cited Ref Sci 1974-1989/Dec
 (c) 1998 Inst for Sci Info
File 55: Biosis, Previews(R) 1993-1999/Sep W2
 (c) 1999 BIOSIS

Set	Items	Description
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? s ctla4?	S1	833 CTLA4?
? s gamma(w)interferon	285654	GAMMA
	114337	INTERFERON
	S2	14115 GAMMA(W) INTERFERON
? s1 and s2	833	S1
	14115	S2
	S3	6 S1 AND S2
? rd		...completed examining records
	S4	6 RD (unique items)
? t s4/3,k,ab/1-6		
4/3,K,AB/1		(Item 1 from file: 155)
DIALOG(R) File 155: MEDLINE(R)		
(c) format only 1999 Dialog Corporation. All rts. reserv.		
08562041 96285769		
The development of effector T cell subsets in murine Leishmania major infection.		
Locksley RM; Wakil AE; Corry DB; Pingel S; Bix M; Fowell DJ		
Department of Medicine, University of California, San Francisco 94143, USA.		
Ciba Found Symp (NETHERLANDS) 1995, 195 p110-7; discussion 117-22,		
ISSN 0300-5208 Journal Code: D7X		
Contract/Grant No.: AI26918, AI, NIAID; AI30663, AI, NIAID; T32 DK07007, DK, NIDDK		
Languages: ENGLISH		
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL		
Leishmania major infection has proven an exceptional model for CD4+ subset development in inbred mice. Most strains contain infection coincident with the appearance of T helper 1 (Th1) cells that produce <u>gamma-interferon (IFN-gamma)</u> required for macrophage activation. In contrast, mice on the BALB background are unable to control infection due to the development of Th2 cells that produce counter-regulatory cytokines, particularly interleukin 4 (IL-4), capable of abrogating the effects of IFN-gamma. Selective gene disruption studies in		

mice have illustrated critical components of the host response to *L. major*. Mice deficient in beta 2 microglobulin, which have no major histocompatibility complex (MHC) class I or CD8+ T cells, control infection as well as wild-type mice, whereas mice deficient in MHC class II (and CD4+ T cells) suffer fatal infection. Mice with disruption of the gene coding IFN-gamma are also incapable of containing infection, reflecting absolute requirements for this cytokine. A number of interventions have been demonstrated to abrogate Th2 cell development in BALB mice, enabling these mice to control infection. Each of these--IL-12, anti-IL-4, anti-IL-2, anti-CD4 and CTLA4-Ig--has in common the capacity to make IL-4 rate limiting at the time of CD4+ cell priming.

...strains contain infection coincident with the appearance of T helper 1 (Th1) cells that produce gamma-interferon (IFN-gamma) required for macrophage activation. In contrast, mice on the BALB background are unable...

...infection. Each of these--IL-12, anti-IL-4, anti-IL-2, anti-CD4 and CTLA4 -Ig--has in common the capacity to make IL-4 rate limiting at the time...

4/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

08188175 94277038

Stat4, a novel gamma interferon activation site-binding protein expressed in early myeloid differentiation.

Yamamoto K; Quelle FW; Thierfelder WE; Kreider BL; Gilbert DJ; Jenkins NA ; Copeland NG; Silvennoinen O; Ihle JN

Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, Tennessee 38105.

Mol Cell Biol (UNITED STATES) Jul 1994, 14 (7) p4342-9, ISSN 0270-7306 Journal Code: NGY

Contract/Grant No.: P30 CA21765, CA, NCI; R01 DK42932, DK, NIDDK; N01 CO-74101, CO, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Interferon regulation of gene expression is dependent on the tyrosine phosphorylation and activation of the DNA-binding activity of two related proteins of 91 kDa (STAT1) and/or 113 kDa (STAT2). Recent studies have suggested that these proteins are substrates of Janus kinases and that proteins related in STAT1 are involved in a number of signalling pathways, including those activated in myeloid cells by erythropoietin and interleukin-3 (IL-3). To clone STAT-related proteins from myeloid cells, degenerate oligonucleotides were used in PCRs to identify novel family members expressed in myeloid cells. This approach allowed the identification and cloning of the Stat4 gene, which is 52% identical to STAT1. Unlike STAT1, Stat4 expression is restricted but includes myeloid cells and spermatogonia. In the erythroid lineage, Stat4 expression is differentially regulated during differentiation. Functionally, Stat4 has the properties of other STAT family genes. In particular, cotransfection of expression constructs for Stat4 and Jak1 and Jak2 results in the tyrosine phosphorylation of Stat4 and the acquisition of the ability to bind to the gamma interferon (IFN-gamma)-activated sequence of the interferon regulatory factor 1 (IRF-1) gene. Stat4 is located on mouse chromosome 1 and is tightly linked to the Stat1 gene, suggesting that the genes arose by gene duplication. Unlike Stat1, neither IFN-alpha nor IFN-gamma activates Stat4. Nor is Stat4 activated in myeloid cells by a number of cytokines, including erythropoietin, IL-3, granulocyte colony-stimulating factor, stem cell factor, colon-stimulating factor 1, hepatocyte growth factor, IL-2, IL-4, and IL-6.

Stat4, a novel gamma interferon activation site-binding

protein expressed in early myeloid differentiation.

... the tyrosine phosphorylation of Stat4 and the acquisition of the ability to bind to the gamma interferon (IFN-gamma)-activated sequence of the interferon regulatory factor 1 (IRF-1) gene. Stat4 is...
Gene Symbol: Stat4; Il1rl; Ctla4; Gls

4/3,K,AB/3 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)
(c) 1999 BIOSIS. All rts. reserv.

11983740 BIOSIS NO.: 199900264259
CTLA4 blockade affects clonal expansion of MBP-reactive T-cells and is dependent on antigen concentration.

AUTHOR: Anderson David E(a); Bieganowska Katarzyna(a); Bar-Or Amit(a); Hafler David A(a)
AUTHOR ADDRESS: (a)Boston, MA, USA

JOURNAL: Neurology 52 (6 SUPPL. 2):pA400-A401 April 12, 1999

CONFERENCE/MEETING: 51st Annual Meeting of the American Academy of Neurology Toronto, Ontario, Canada April 17-24, 1999
SPONSOR: American Academy of Neurology

ISSN: 0028-3878

RECORD TYPE: Citation

LANGUAGE: English

CTLA4 blockade affects clonal expansion of MBP-reactive T-cells and is dependent on antigen concentration.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...**CTLA4**; ...

...IFN gamma (interferon gamma

4/3,K,AB/4 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)
(c) 1999 BIOSIS. All rts. reserv.

11729581 BIOSIS NO.: 199800511312

Regulation of T helper cell differentiation in vivo by soluble and membrane proteins provided by antigen-presenting cells.

AUTHOR: De Becker Genevieve; Moulin Veronique; Tielemans Francoise; De Mattia Fabrizio; Urbain Jacques; Leo Oberdan; Moser Muriel(a)
AUTHOR ADDRESS: (a)Lab. Physiol. Anim., Univ. Libre Bruxelles, Rue des Chevaux 67, B-1640 Rhode-saint-Genese, Belgium

JOURNAL: European Journal of Immunology 28 (10):p3161-3171 Oct., 1998

ISSN: 0014-2980

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The aim of this study was to test whether the nature of the antigen-presenting cell (APC) can influence the Th1/Th2 balance in vivo. Our data show that dendritic cells (DC), pulsed-extracorporeally with antigen, induced the development of cells secreting IL-2, IFN-gamma and IL-4 upon antigen rechallenge in vitro. Priming with peritoneal macrophages sensitized cells that produced IL-4 but not IFN-gamma. To identify the factors involved in T helper development, mice were primed with APC with or without treatment with neutralizing antibodies to costimulatory molecules or cytokines. Our results indicate that priming

with DC or macrophages is strictly dependent on the CD28-CTLA4/B7 interaction. Of note, CD86 provides the initial signal to induce naive T cells to become IL-4 producers, whereas CD80 is a more neutral differentiation signal. IL-12, released by the DC, appears as a potent and obligatory inducer of differentiation for IFN-gamma-producing cells. IL-6, although produced by both APC populations, is necessary to direct activation of the Th2-type response by macrophages but not by DC.

...ABSTRACT: Our results indicate that priming with DC or macrophages is strictly dependent on the CD28-CTLA4/B7 interaction. Of note, CD86 provides the initial signal to induce naive T cells to...

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...INF-gamma {interferon-gamma}

4/3,K,AB/5 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

11715293 BIOSIS NO.: 199800497024
Blockade of CD28/B7 interaction suppresses allergic eosinophilic inflammation in mice.

AUTHOR: Kasai Masaaki; Kumano Koutaro; Kurasawa Kazuhiro; Nakao Atsuhito; Saito Yasushi; Iwamoto Itsuo(a)

AUTHOR ADDRESS: (a)Dep. Internal Med. II, Chiba Univ. Sch. Med., 1-8-1 Inohana, Chiba City, Chiba 260, Japan

JOURNAL: International Archives of Allergy and Immunology 117 (SUPPL. 1):p 14-19 Sept., 1998

ISSN: 1018-2438

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: To determine whether the costimulatory signal via CD28/B7 interaction is required for causing allergic inflammation, we examined the effect of administration of CTLA4-Ig, a fusion protein of the extracellular domain of CTLA4 and human IgG1-constant region, at the time of sensitization, on antigen-induced eosinophil infiltration in the trachea of sensitized mice, on IL-2, IFNgamma, IL-4 and IL-5 production in the airways of the mice and on antigen-specific IgE synthesis in the mice. Administration of CTLA4-Ig at the time of sensitization suppressed antigen-induced eosinophil infiltration into the trachea and antigen-specific IgE production in mice. Furthermore, CTLA4-Ig administration at the time of sensitization suppressed not only IL-2 production but also IFN-gamma and Th2 cytokine IL-4 and IL-5 production in the airways. Because allergic inflammation requires CD4+ T cells producing Th2-type cytokines IL-4 and IL-5, our results suggest that the costimulatory signal via CD28/B7 interaction is important for the generation and activation of Th2 cells and thereby for the development of allergic inflammation.

...ABSTRACT: B7 interaction is required for causing allergic inflammation, we examined the effect of administration of CTLA4-Ig, a fusion protein of the extracellular domain of CTLA4 and human IgG1-constant region, at the time of sensitization, on antigen-induced eosinophil infiltration...

...airways of the mice and on antigen-specific IgE synthesis in the mice. Administration of CTLA4-Ig at the time of sensitization suppressed antigen-induced eosinophil infiltration into the trachea and antigen-specific IgE production in mice. Furthermore, CTLA4-Ig administration at the time of sensitization suppressed not only IL-2 production but also...

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...CTLA4-Ig...

...IFN-gamma {interferon-gamma}

4/3,K,AB/6 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Preivviews(R)
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11447500 BIOSIS NO.: 199800228832
CD28-independent induction of T helper cells and immunoglobulin class switches requires costimulation by the heat-stable antigen.

AUTHOR: Wu Yan; Zhou Qunmin; Zheng Pan; Liu Yang(a)

AUTHOR ADDRESS: (a)Michael Heidelberger Div. Immunol., Dep. Pathol. Kaplan Comprehensive Cancer Cent., New York Uni, USA

JOURNAL: Journal of Experimental Medicine 187 (7):p1151-1156 April 6, 1998
ISSN: 0022-1007

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: It is well established that B7-CD28/CTLA4 interactions play an important role in the induction of T helper cells for T-dependent antibody responses. However, targeted mutation of CD28 does not significantly affect production of IgG and activation of CD4 T helper cells in response to infections by some viruses and nematode parasites. To test whether the CD28-independent induction of Ig class switches requires costimulation by the heat-stable antigen (HSA), we compared T helper cell induction and antibody response in mice deficient for either HSA, CD28, or both genes. We found that after immunization with KLH-DNP, mice deficient for both CD28 and HSA lack DNP-specific IgA and all subtypes of IgG. This deficiency corresponds to a reduced number of effector helper T cells that rapidly produce IL-2, IL-4, and IFN-gamma after in vitro stimulation with carrier antigen KLH. In contrast, priming of T helper cells and Ig class switch are normal in mice deficient with either HSA or CD28 alone. IgM responses are not affected by any of these targeted mutations. These results demonstrate that CD28-independent induction of T helper cells and Ig class-switches requires costimulation by the HSA.

ABSTRACT: It is well established that B7-CD28/CTLA4 interactions play an important role in the induction of T helper cells for T-dependent...
DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...IFN-gamma {interferon-gamma...}

CHEMICALS & BIOCHEMICALS: ...IFN-gamma {interferon-gamma...
? ds

Set Items Description
S1 833 CTLA4?
S2 14115 GAMMA(W) INTERFERON
S3 6 S1 AND S2
S4 6 RD (unique items)
? s complement
 S5 114256 COMPLEMENT
? s s1 and s5
 833 S1
 114256 S5
 S6 4 S1 AND S5
? rd
...completed examining records
 S7 3 RD (unique items)
? t s7/3,k,ab/1-3

7/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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09359806 98069530
[Is there a place for gene therapy in organ transplantation?] Existe-t-il une place pour la therapie genique en transplantation d'organes?
Gianello P
Laboratoire de Chirurgie Experimentale, Universite Catholique de Louvain en Woluwe, Bruxelles, Belgique.
Ann Chir (FRANCE) 1997, 51 (6) p593-604, ISSN 0003-3944
Journal Code: 50E
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English
Abstract

The major research objectives in organ transplantation are to palliate the lack of organs, to decrease the adverse effects of chronic immunosuppression and to improve medium-term and long-term graft survival. Xenotransplantation and induction of a permanent and specific tolerance to an allograft therefore represent two main lines of research which could partly resolve the problems of organ transplantation. The objective of this article is to evaluate the possible role of gene therapy in the development of xenotransplantation and induction of allograft tolerance. They review the various gene vectors currently available as well as the routes of administration of these vectors specific to transplantation. The place of gene therapy is then evaluated in the context of allo- and xenotransplantation. In allotransplantation, transfection of certain genes of interest into the transplant organ before implantation or into the recipient's immune system is considered. Transfection into the transplant organ of genes coding for immunomodulating cytokines (TGF-beta, IL-4, IL-10, etc.), molecules which block the second signal (CTLA4-Ig) or molecules responsible for apoptosis (Fas/FasL) is discussed. The value of gene therapy in the recipient's immune system consists of transfection onto the recipient's bone marrow cells of genes coding for major histocompatibility system molecules (HLA-DR, DQ, etc.). In xenotransplantation, gene therapy will certainly play a major role in the development of transgenic pigs expressing, on the surface endothelium of their organs, certain human molecules which regulate the activity of complement (CD55, CD59, etc.) or which modify the expression of

glycosylated xenoantigens (alpha-galactosyl) recognized by performed antibodies.

... immunomodulating cytokines (TGF-beta, IL-4, IL-10, etc.), molecules which block the second signal (CTLA4-Ig) or molecules responsible for apoptosis (Fas/FasL) is discussed. The value of gene therapy...

... on the surface endothelium of their organs, certain human molecules which regulate the activity of complement (CD55, CD59, etc.) or which modify the expression of glycosylated xenoantigens (alpha-galactosyl) recognized by...

7/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
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10/29/99

08423204 95363081

Ex vivo coating of islet cell allografts with murine CTLA4/Fc promotes graft tolerance.

Steurer W; Nickerson PW; Steele AW; Steiger J; Zheng XX; Strom TB
Harvard Medical School, Department of Medicine, Boston, MA, USA.
J Immunol (UNITED STATES) Aug 1 1995; 155 (3) p1165-74, ISSN
0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

To test the hypothesis that blockade of B7-triggered costimulation by donor cells could preclude allograft rejection, we coated crude islet allograft preparations in vitro for 1 h with a murine CTLA4/Fc fusion protein. Murine CTLA4/Fc blocks the proliferative response in primary mixed lymphocyte cultures (MLC) and Con A-stimulated murine spleen cell cultures by 85 to 95%. Responder cells from a primary MLC containing mCTLA4/Fc were hyporesponsive upon restimulation to the same stimulator cells in a secondary MLC lacking mCTLA4/Fc. Because of mutations in the Fc gamma RI and C'1q binding sites of the Fc portion of the murine CTLA4/Fc fusion protein, the molecule binds to, but does not target, cells for Ab-dependent cellular cytotoxicity or complement-directed cytolysis. Although systemic immunosuppression was not applied, 42% (10 of 24) of B6AF1 recipients of islet allografts pretreated with CTLA4/Fc were permanently engrafted. Further, 50% of hosts bearing functioning islet allografts more than 150 days post-transplant were formally proved to be tolerant to donor tissues. A persistent CD4+ and CD8+ T cell infiltrate surrounding, but not invading, islet grafts in tolerant hosts was discerned. In control experiments, 89% (8 of 9) of islet allografts coated with mIgG3, and 100% (n = 10) pretreated with media alone were rejected. Thus, we conclude that 1) B7-triggered costimulation by donor APCs is an important element of rejection, and 2) blockade of the B7 pathway by in vitro allograft manipulation is able to induce tolerance.

Ex vivo coating of islet cell allografts with murine CTLA4/Fc promotes graft tolerance.

... rejection, we coated crude islet allograft preparations in vitro for 1 h with a murine CTLA4/Fc fusion protein. Murine CTLA4/Fc blocks the proliferative response in primary mixed lymphocyte cultures (MLC) and Con A-stimulated...

...Fc gamma RI and C'1q binding sites of the Fc portion of the murine CTLA4 /Fc fusion protein, the molecule binds to, but does not target, cells for Ab-dependent cellular cytotoxicity or complement-directed cytolysis. Although systemic immunosuppression was not applied, 42% (10 of 24) of B6AF1 recipients of islet allografts pretreated with CTLA4/Fc were permanently engrafted. Further, 50% of hosts bearing functioning islet allografts more than 150...

7/3,K,AB/3 (Item 1 from file: 55)

DIALOG(R)File 55:Biosis Preiviews(R)
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10369763 BIOSIS NO.: 199698824681
Interactions of CD80 and CD86 with CD28 and CTLA4.

AUTHOR: Ellis Jonathan H(a); Burden M Neil; Vinogradov Dimitri V; Linge Claire; Crowe J Scott
AUTHOR ADDRESS: (a)Immunopathol. Unit, Glaxo-Wellcome Med. Res. Cent., Gunnels Wood Road, Stevenage, Hertfordshire , UK

JOURNAL: Journal of Immunology 156 (8):p2700-2709 1996

ISSN: 0022-1767

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: CD80 and CD86 are cell surface glycoproteins expressed on a variety of professional APCs. They have attracted much attention due to their function as potent costimulators of T lymphocyte function through their interaction with CD28 and possibly CTLA4. Because inhibitors of this interaction may have therapeutic relevance in human autoimmune disease, we investigated the properties of linear peptides derived from conserved regions of CTLA4 and CD80 known to be essential for binding. None of these peptides were sufficient to bind ligand, nor did they act as potent competitive inhibitors. Conformationally constrained versions of the CTLA4 motif were also inactive. These results suggested that other parts of the proteins are important in determining binding, so a series of modified CD80 and CD86 molecules were constructed in an attempt to identify other binding determinants. Insertion of two residues between the two Ig domains of CD80 resulted in decreased affinity for CTLA4, but a similar mutation in CD86 was without effect. We also identified another asymmetry between CD80 and CD86 in that the V domain of CD86 but not that of CD80 is sufficient for CTLA4 binding. The CD86-V domain appears to have CTLA4 binding properties equivalent to that of intact CD86. These data illustrate a fundamental difference between these costimulatory molecules and suggest a mechanism by which they may be differentially recognized by receptors on the T cell surface.

Interactions of CD80 and CD86 with CD28 and CTLA4.

...ABSTRACT: function as potent costimulators of T lymphocyte function through their interaction with CD28 and possibly CTLA4. Because inhibitors of this interaction may have therapeutic relevance in human autoimmune disease, we investigated the properties of linear peptides derived from conserved regions of CTLA4 and CD80 known to be essential for binding. None of these peptides were sufficient to bind ligand, nor did they act as potent competitive inhibitors. Conformationally constrained versions of the CTLA4 motif were also inactive. These results suggested that other parts of the proteins are important...

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...in that the V domain of CD86 but not that of CD80 is sufficient for CTLA4-binding. The CD86-V domain appears to have CTLA4 binding properties equivalent to that of intact CD86. These data illustrate a fundamental difference between...

MISCELLANEOUS TERMS: COMPLEMENT;

ds

Set	Items	Description
S1	833	CTLA4?
S2	14115	GAMMA(W) INTERFERON
S3	6	S1 AND S2
S4	6	RD (unique items)
S5	114256	COMPLEMENT
S6	4	S1 AND S5
S7	3	RD (unique items)

? s interferon
S8 114337 INTERFERON

? s s1 and s8
833 S1
114337 S8
S9 79 S1 AND S8

? s gamma
S10 285654 GAMMA

? s s9 and s10
79 S9
285654 S10
S11 74 S9 AND S10

? s s11 not s3
74 S11
6 S3
S12 68 S11 NOT S3

? s increas?
S13 1944665 INCREAS?

? s s12 and s13
68 S12
1944665 S13
S14 20 S12 AND S13

? rd
...completed examining records
S15 12 RD (unique items)

? t s15/3,k,ab/1-12

15/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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09782490 99077174
CTLA4 (CD152) modulates the Th subset response and alters the course of experimental Leishmania major infection.
Saha B; Chattopadhyay S; Germond R; Harlan DM; Perrin PJ
Immune Cell Biology Program, Naval Medical Research Institute, Bethesda,
USA. root@nccs.ernet.in
Eur J Immunol (GERMANY) Dec 1998, 28 (12) p4213-20, ISSN 0014-2980
Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Since both the nature and the amplitude of an antigen-specific T cell response are dependent on co-stimulatory signals, we have investigated the role of CD28/CD152-mediated T cell co-stimulation in the regulation of experimental cutaneous leishmaniasis. CD28-deficient mice and their wild-type littermates are equally susceptible to Leishmania major infection. Whole anti-CD152 antibody significantly exacerbates the disease while anti-CD152 Fab ameliorates the disease in genetically susceptible BALB/c mice but not in C57BL/6, a resistant strain. The anti-CD152-induced

exacerbation of the disease is accompanied by increased IL-4-secreting cell number, diminished parasite-specific delayed-type hypersensitivity (DTH) response and augmented anti-2,4,6-trinitrophenyl (TNP) IgG1 in response to TNP-leishmanial antigen crude soluble antigen (CSA), suggesting an exaggerated Th2 type of response. Anti-CD152 Fab-mediated amelioration of the disease is associated with increased IFN-gamma-secreting cell number, increased parasite-specific DTH response and enhanced IgG2a isotype in response to TNP-CSA suggesting a Th1 type of response. Unlike TNP-CSA, TNP-keyhole limpet hemocyanin does not induce the change in Ig isotype, indicating that the immunomodulatory effect of anti-CD152 is antigen specific. Anti-CD152 antibody-induced early change in Th subsets suggests an important role for CD152 in determining the course of *L. major* infection, perhaps by alteration of Th subset differentiation.

CTLA4 (CD152) modulates the Th subset response and alters the course of experimental *Leishmania major* infection.

... 6, a resistant strain. The anti-CD152-induced exacerbation of the disease is accompanied by increased IL-4-secreting cell number, diminished parasite-specific delayed-type hypersensitivity (DTH) response and augmented...

... Th2 type of response. Anti-CD152 Fab-mediated amelioration of the disease is associated with increased IFN-gamma-secreting cell number, increased parasite-specific DTH response and enhanced IgG2a isotype in response to TNP-CSA suggesting a...

; Interferon Type II--Immunology--IM; Interleukin-4--Immunology--IM
; Mice; Mice, Inbred BALB C; Mice, Inbred...
Chemical Name: Antigens, Differentiation; (CTLA-4; (Interleukin-4; (Interferon Type II

15/3,K,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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09721994 99008514

CD40 ligand/trimer DNA enhances both humoral and cellular immune responses and induces protective immunity to infectious and tumor challenge.

Gurunathan S; Irvine KR; Wu CY; Cohen JI; Thomas E; Prussin C; Restifo NP
; Seder RA

Clinical Immunology Section, Laboratory of Clinical Investigation,
National Institute of Allergy and Infectious Diseases, National Institutes
of Health, Bethesda, MD 20892, USA.

J Immunol (UNITED STATES) Nov 1 1998, 161 (9) p4563-71, ISSN
0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

CD40/CD40 ligand interactions have a central role in the induction of both humoral and cellular immunity. In this study, we examined whether a plasmid expressing CD40 ligand/trimer (CD40LT) could enhance immune responses in vivo. BALB/c mice were injected with plasmid expressing beta-galactosidase DNA with or without CD40LT DNA or IL-12 DNA, and immune responses were assessed. Mice vaccinated with beta-gal DNA plus CD40LT DNA or IL-12 DNA had a striking increase in Ag-specific production of IFN-gamma, cytolytic T cell activity, and IgG2a Ab. The mechanism by which CD40LT DNA enhanced these responses was further assessed by treating vaccinated mice with anti-IL-12 mAb or CTLA-4 Ig (CTLA4 Ig). Production of IFN-gamma and CTL activity was abrogated by these treatments, suggesting that CD40LT DNA was mediating its effects on IFN-gamma and CTL activity through induction of IL-12 and enhancement of B7 expression, respectively. Physiologic relevance for the ability of CD40LT DNA to enhance immune responses by the aforementioned pathways was shown in two in vivo models. First, with regard to CTL activity, mice

vaccinated with CD40LT DNA did not develop metastatic tumor following challenge with lethal dose of tumor. Moreover, in a mouse model requiring IL-12-dependent production of IFN-gamma, mice vaccinated with soluble Leishmania Ag and CD40LT DNA were able to control infection with Leishmania major. These data suggest that CD40LT DNA could be a useful vaccine adjuvant for diseases requiring cellular and/or humoral immunity.

... vaccinated with beta-gal DNA plus CD40LT DNA or IL-12 DNA had a striking increase in Ag-specific production of IFN-gamma, cytolytic T cell activity, and IgG2a Ab. The mechanism by which CD40LT DNA enhanced these...

... further assessed by treating vaccinated mice with anti-IL-12 mAb or CTLA-4 Ig (CTLA4Ig). Production of IFN-gamma and CTL activity was abrogated by these treatments, suggesting that CD40LT DNA was mediating its effects on IFN-gamma and CTL activity through induction of IL-12 and enhancement of B7 expression, respectively. Physiologic...

... dose of tumor. Moreover, in a mouse model requiring IL-12-dependent production of IFN-gamma, mice vaccinated with soluble Leishmania Ag and CD40LT DNA were able to control infection with...

...; Colonic Neoplasms--Pathology--PA; Cytotoxicity, Immunologic; DNA, Recombinant--Pharmacology--PD; Genes, Reporter; IgG--Biosynthesis--BI; Interferon Type II--Biosynthesis--BI; Interleukin-12--Genetics--GE; Interleukin-12--Physiology--PH; Leishmania major--Immunology...

...Chemical Name: Neoplasm; (Antigens, CD28; (Antigens, CD80; (DNA, Recombinant; (IgG; (Interleukin-12; (Membrane Glycoproteins; (Vaccines, Synthetic; (CD40L; (Interferon Type II

15/3,K,AB/3 (Item 3 from file: 155)

DIALOG(R) File 155: MEDLINE(R)

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09696408 98202492

10/29/99

CTLA4Ig inhibits airway eosinophilia and hyperresponsiveness by regulating the development of Th1/Th2 subsets in a murine model of asthma.

Padrid PA; Mathur M; Li X; Herrmann K; Qin Y; Cattamanchi A; Weinstock J; Elliott D; Sperling AI; Bluestone JA

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Am J Respir Cell Mol Biol (UNITED STATES) Apr 1998, 18 (4) p453-62, ISSN 1044-1549 Journal Code: AOB

Contract/Grant No.: HL 56399-01, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Complete T-cell activation requires two distinct signals, one delivered via the T-cell receptor, and the second "co-stimulatory" signal through CD28/B7 ligation. Previous studies showed that the blockade of CD28/B7 ligation alters differentiation of Th1/Th2 lymphocyte subsets in vitro and in vivo. The present study was designed to determine the effect of a CD28/B7 antagonist (CTLA4Ig) on Th1/Th2 development in Schistosoma mansoni-sensitized and airway-challenged mice. Treatment of mice with CTLA4Ig beginning 1 wk after sensitization abolished airway responsiveness to intravenous methacholine determined 96 h following antigen challenge. We also found a significant reduction in bronchoalveolar lavage (BAL) eosinophilia, and reduced peribronchial eosinophilic infiltration and mucoid-cell hyperplasia. Furthermore, CTLA4Ig treatment significantly decreased interleukin (IL)-4 and IL-5 content in BAL fluid in vivo, and the production of IL-5 by lung lymphocytes stimulated with soluble egg antigen (SEA) in vitro. In contrast, the content of interferon-gamma in BAL fluid and supernatant from SEA-stimulated lung lymphocytes from CTLA4Ig-treated mice was increased significantly compared with untreated animals. Thus, CTLA4Ig inhibits eosinophilic airway inflammation and airway

hyperresponsiveness in *S. mansoni*-sensitized and airway-challenged mice, most likely due to attenuated secretion of Th2-type cytokines and increased secretion of Th1-type cytokines.

CTLA4Ig inhibits airway eosinophilia and hyperresponsiveness by regulating the development of Th1/Th2 subsets in a...

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15/3,K,AB/4 (Item 4 from file: 155)

DIALOG(R) File 155: MEDLINE(R)

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09597501 98317030

Cytotoxic T lymphocyte antigen 4 (**CTLA4**) blockade accelerates the acute rejection of cardiac allografts in CD28-deficient mice: **CTLA4** can function independently of CD28.

Lin H; Rathmell JC; Gray GS; Thompson CB; Leiden JM; Alegre ML
Department of Medicine, University of Chicago, Chicago, Illinois 60637,
USA.

J Exp Med (UNITED STATES) Jul 6 1998, 188 (1) p199-204, ISSN
0022-1007 Journal Code: I2V

Contract/Grant No.: R37AI29637, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Cytotoxic T lymphocyte antigen 4 (**CTLA4**) appears to negatively regulate T cell activation. One mechanism by which **CTLA4** might antagonize T cell function is through inhibition of CD28 signaling by competing for their shared ligands B7-1 and B7-2. In addition, **CTLA4** ligation could initiate a signaling cascade that inhibits T cell activation. To address whether **CTLA4** could inhibit immune responses in the absence of CD28, rejection of heart allografts was studied in CD28-deficient mice. H-2(q) hearts were transplanted into allogeneic wild-type or CD28-deficient mice (H-2(b)). Graft rejection was delayed in CD28-deficient compared with wild-type mice. Treatment of wild-type recipients with **CTLA4** -immunoglobulin (Ig), or with anti-B7-1 plus anti-B7-2 mAbs significantly prolonged allograft survival. In contrast, treatment of CD28-deficient mice with **CTLA4** -Ig, anti-B7-1 plus anti-B7-2 mAbs, or a blocking anti-**CTLA4** mAb induced acceleration of allograft rejection. This increased rate of graft rejection was associated with more severe mononuclear cell infiltration and enhanced levels of IFN-gamma and IL-6 transcripts in donor hearts of untreated wild-type and **CTLA4**-Ig- or anti-**CTLA4** mAb-treated CD28-deficient mice. Thus, the negative regulatory role of **CTLA4** extends beyond its potential ability to prevent CD28 activation through ligand competition. Even in the absence of CD28, **CTLA4** plays an inhibitory role in the regulation of allograft rejection.

Cytotoxic T lymphocyte antigen 4 (CTLA4) blockade accelerates the acute rejection of cardiac allografts in CD28-deficient mice: CTLA4 can function independently of CD28.

Cytotoxic T lymphocyte antigen 4 (CTLA4) appears to negatively regulate T cell activation. One mechanism by which CTLA4 might antagonize T cell function is through inhibition of CD28 signaling by competing for their shared ligands B7-1 and B7-2. In addition, CTLA4 ligation could initiate a signaling cascade that inhibits T cell activation. To address whether CTLA4 could inhibit immune responses in the absence of CD28, rejection of heart allografts was studied...

... delayed in CD28-deficient compared with wild-type mice. Treatment of wild-type recipients with CTLA4-immunoglobulin (Ig), or with anti-B7-1 plus anti-B7-2 mAbs significantly prolonged allograft survival. In contrast, treatment of CD28-deficient mice with CTLA4-Ig, anti-B7-1 plus anti-B7-2 mAbs, or a blocking anti-CTLA4 mAb induced acceleration of allograft rejection. This increased rate of graft rejection was associated with more severe mononuclear cell infiltration and enhanced levels of IFN-gamma and IL-6 transcripts in donor hearts of untreated wild-type and CTLA4-Ig- or anti-CTLA4 mAb-treated CD28-deficient mice. Thus, the negative regulatory role of CTLA4 extends beyond its potential ability to prevent CD28 activation through ligand competition. Even in the absence of CD28, CTLA4 plays an inhibitory role in the regulation of allograft rejection.

...; PD; Antigens, CD28--Genetics--GE; Antigens, Differentiation --Immunology--IM; Flow Cytometry; Graft Survival--Immunology--IM; Interferon Type II--Genetics--GE; Isoantigens--Pharmacology--PD; Mice ; Mice, Knockout; Myocardium--Pathology--PA; Recombinant Fusion...

Chemical Name: Antibodies, Monoclonal; (Antigens, CD28; (Antigens, Differentiation; (CTLA-4; (Isoantigens; (Recombinant Fusion Proteins; (Interferon Type II

15/3, K, AB/5 (Item 5 from file: 155)

DIALOG(R) File 155: MEDLINE(R)

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09497636 98240962

Arterial and venular endothelial cell costimulation of cytokine secretion by human T cell clones.

Johnson DR; Hauser IA; Voll RE; Emmrich F
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Germany. johnson@biomed.med.yale.edu
J Leukoc Biol (UNITED STATES) May 1998, 63 (5) p612-9, ISSN 0741-5400
Journal Code: IWY

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Vascular endothelial cell (EC) costimulation of cytokine secretion by T lymphocytes may be important in inflammation and allograft rejection. Venous and arterial iliac endothelial cells (VIEC, AIEC) both costimulate interleukin-2 (IL-2) production by peripheral blood lymphocytes (PBL) or T cell clones stimulated with phytohemagglutinin (PHA). Interferon-gamma (IFN-gamma) production is costimulated in a subset of clones but IL-4 is not. Surprisingly, two T cell clones were reciprocally better costimulated by VIEC or AIEC. EC activation by pretreatment with tumor necrosis factor alpha (TNF-alpha) does not increase T cell costimulation despite large increases in EC cell adhesion molecule expression. Neither VIEC nor AIEC express CTLA4-binding molecules and costimulation is blocked by cyclosporin A, suggesting that CD28 is not involved in EC costimulation of T cells. These data suggest that adult vascular EC costimulate production of IL-2 and IFN-gamma but not IL-4 by mature T cells, that EC costimulation is not increased in inflamed tissues, and that different EC optimally costimulate particular T cells. These findings have implications for the nature of the costimulatory

signal(s) provided by EC and may be important in understanding vasculitis or atherosclerosis.

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; Antigens, Differentiation--Pharmacology--PD; Arteries--Cytology--CY; Cells, Cultured; Clone Cells; Cyclosporine--Pharmacology--PD; Immunophenotyping; Interferon Type II--Biosynthesis--BI; Interleukin-2--Biosynthesis--BI; Interleukin-4--Biosynthesis--BI; Tumor Necrosis Factor...

Chemical Name: Antigens, Differentiation; (Cytokines; (CTLA-4; (Interleukin-2; (Interleukin-4; (Tumor Necrosis Factor; (Cyclosporine; (Interferon Type II

15/3,K,AB/6 (Item 6 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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09485245 98206877

Immunoliposomes containing antibodies to costimulatory molecules as adjuvants for HIV subunit vaccines.

Ozpolat B; Rao XM; Powell MF; Lachman LB

Department of Cell Biology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

AIDS Res Hum Retroviruses (UNITED STATES) Mar 20 1998, 14 (5) p409-17, ISSN 0889-2229 Journal Code: ART

Contract/Grant No.: CA16672, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Immunoliposomes containing monoclonal antibodies (MAbs) to the costimulatory molecules CD28 and CTLA4 and their counterreceptors B7-1 (CD80) and B7-2 (CD86) were evaluated for the ability to increase the immune response to recombinant envelope protein rgp120 of the MN strain of human immunodeficiency virus type 1 (HIV-1) during vaccination. MAbs were attached to rgp120-containing liposomes via a biotin-avidin-biotin bridge. Mice vaccinated with immunoliposomes were found to have a strong delayed-type hypersensitivity (DTH) response to the weakly immunogenic gp120 that was dependent on the presence of the MAbs. However, this vaccination protocol did not induce humoral immunity. The DTH response was not accompanied by increased production of interferon gamma (IFN-gamma) or interleukin 4 (IL-4), implying that the primary cellular interaction was between the immunoliposomes and cells of the reticuloendothelial system and not helper T (Th) cells. This strategy of incorporating antibodies to costimulatory molecules on the surface of antigen-containing particulates, such as liposomes or microspheres, can be used to increase DTH immune responses to protein or peptide vaccines.

Immunoliposomes containing monoclonal antibodies (MAbs) to the costimulatory molecules CD28 and CTLA4 and their counterreceptors

B7-1 (CD80) and B7-2 (CD86) were evaluated for the ability to increase the immune response to recombinant envelope protein gp120 of the MN strain of human immunodeficiency...

... this vaccination protocol did not induce humoral immunity. The DTH response was not accompanied by increased production of interferon gamma (IFN-gamma) or interleukin 4 (IL-4), implying that the primary cellular interaction was between the immunoliposomes...

... the surface of antigen-containing particulates, such as liposomes or microspheres, can be used to increase DTH immune responses to protein or peptide vaccines.

...; CD80--Immunology--IM; Hypersensitivity, Delayed--Immunology--IM; IgG --Blood--BL; IgG--Isolation and Purification--IP; Interferon Type II --Immunology--IM; Liposomes--Metabolism--ME; Mice; Mice, Inbred C3H; Middle Age

...Chemical Name: CD80; (AIDS Vaccines; (HIV Antibodies; (HIV Antigens; (HIV Envelope Protein gp120; (IgG; (Liposomes; (Vaccines, Synthetic; (Interferon Type II

15/3,K,AB/7 (Item 7 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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09404077 98124446

Blockade of CD40-CD40 ligand pathway induces tolerance in murine contact hypersensitivity.

Tang A; Judge TA; Turka LA

Department of Medicine and Institute for Human Gene Therapy, University of Pennsylvania, Philadelphia 19104-6100, USA.

Eur J Immunol (GERMANY) Dec 1997, 27 (12) p3143-50, ISSN 0014-2980
Journal Code: EN5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Interactions between CD40 on antigen-presenting cells and its ligand (CD40L) on T cells has been implicated in T cell-mediated immune responses. Previously, we have shown that contact hypersensitivity (CHS), a cell-mediated cutaneous immune response in reaction to haptens, could be subclassified based on whether the hapten primed for Th1 or Th2 cytokines in cells isolated from draining lymph nodes. We also found that tolerance to a Th2-priming hapten could be induced only by simultaneous blockade of the CD40-CD40L and B7-CD28 at the time of sensitization. Here we demonstrate that blockade of CD40-CD40L signaling alone induces long-lasting unresponsiveness to the Th1 hapten 2,4-dinitrofluorobenzene (DNFB), and inhibits antigen-specific T cell proliferation in vitro. We find that CD40-CD40L signaling is required in the sensitization but not elicitation phase of DNFB-induced CHS, as treatment of mice with anti-CD40L monoclonal antibody (mAb) does not affect the response to hapten challenge in previously sensitized and untreated animals. Examination of cytokine production shows that anti-CD40L mAb decreases interferon-gamma production by draining lymph node cells from DNFB-sensitized mice, and reciprocally increases interleukin (IL)-4 production. Consistent with this Th1 to Th2 immune deviation, anti-CD40L mAb prevents the induction of IL-12 mRNA in regional lymph nodes, an event which is normally seen within 12 h following hapten sensitization. In contrast, suppression of CHS by CTLA4Ig decreased the production of all cytokines by draining lymph node cells. Together, these data show that blockade of the CD40-CD40L pathway by itself is sufficient to induce tolerance to DNFB-induced CHS, and that this is associated with blockade of IL-12 induction and Th1 to Th2 immune deviation.

... previously sensitized and untreated animals. Examination of cytokine production shows that anti-CD40L mAb decreases interferon-gamma

production by draining lymph node cells from DNFB-sensitized mice, and reciprocally increases interleukin (IL)-4 production. Consistent with this Th1 to Th2 immune deviation, anti-CD40L mAb...
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15/3, K, AB/8 (Item 8 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
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08968654 97188391

The role of the CD28/B7 interaction in the regulation of NK cell responses during infection with *Toxoplasma gondii*.

Hunter CA; Ellis-Neyer L; Gabriel KE; Kennedy MK; Grabstein KH; Linsley PS; Remington JS

Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia 19104, USA.

J Immunol (UNITED STATES) Mar 1 1997, 158 (5) p2285-93, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI04717, AI, NIAID; AI30320, AI, NIAID; AI41158, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We examined the role of the CD28/B7 interaction in regulation of NK cell activity. Cells transfected with B7 enhanced IL-12-induced production of IFN-gamma by IL-2-activated, CD28+ NK cells, but not by resting CD28- NK cells. The ability of B7 transfectants to enhance NK cell production of IFN-gamma was dependent on the intracellular adhesion molecule-1/LFA-1 interaction and could be inhibited by TGF-beta, but not IL-10. Since IL-12-induced production of IFN-gamma by NK cells is associated with resistance to certain infections, we examined whether the CD28/B7 interaction regulated NK cell responses during infection. Infection of SCID mice with *Toxoplasma gondii* resulted in the appearance of a population of CD28+ NK cells, NK cell production of IFN-gamma, and increased NK cell cytolytic activity. Administration of CTLA4-Ig to SCID mice infected with *T. gondii* inhibited these latter two effects and resulted in a significant increase in parasite burden. The stimulus for CD28 expression by NK cells in SCID mice infected with *T. gondii* appeared to be independent of IL-2. However, mRNA for IL-15, a cytokine with properties similar to those of IL-2, was detected in tissues of SCID mice infected with *T. gondii*. In vitro experiments demonstrated that IL-15 could stimulate resting NK cells to express functionally active CD28 as well as enhance the production of IFN-gamma by SCID splenocytes stimulated with *T. gondii*. Together our data demonstrate that the interaction of CD28+ NK cells with B7 regulates NK cell production of IFN-gamma associated with resistance to infection and that IL-15 may be involved in these events.

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... NK cells to express functionally active CD28 as well as enhance the production of IFN-gamma by SCID splenocytes stimulated with T. gondii. Together our data demonstrate that the interaction of CD28+ NK cells with B7 regulates NK cell production of IFN-gamma associated with resistance to infection and that IL-15 may be involved in these events.

...; GE; Antigens, Differentiation--Administration and Dosage--AD; Injections, Intraperitoneal; Intercellular Adhesion Molecule-1--Physiology --PH; Interferon Type II--Biosynthesis--BI; Interleukin-10 --Physiology--PH; Interleukin-12--Pharmacology--PD; Interleukin-15 --Physiology...

...Chemical Name: Lymphocyte Function-Associated Antigen-1; (Transforming Growth Factor beta; (Intercellular Adhesion Molecule-1; (Interleukin-10; (Interferon Type II

15/3,K,AB/9 (Item 9 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08695355 96235157

Opposing effects of CTLA4-Ig and anti-CD80 (B7-1) plus anti-CD86 (B7-2) on experimental allergic encephalomyelitis.

Perrin PJ; Scott D; Davis TA; Gray GS; Doggett MJ; Abe R; June CH; Racke MK

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J Neuroimmunol (NETHERLANDS) Mar 1996, 65 (1) p31-9, ISSN 0165-5728
Journal Code: HSO

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The roles of the B7 receptors, CD80 and CD86, during actively induced experimental allergic encephalomyelitis were examined with specific monoclonal antibodies and CTLA4-Ig. Injection of CTLA4-Ig on day 2 post-immunization resulted in decreased incidence and severity of resultant disease. Anti-CD80 injection on day 2 blocked development of the first disease episode. Subsequent relapses were unaffected. In contrast, injection of anti-CD86 alone had no effect. Surprisingly, combined anti-CD80 + anti-CD86 monoclonal antibody injection on day 2 resulted in marked exacerbation of disease. Examination of cytokine production in the draining lymph node cells demonstrated a reduction in both interferon (IFN)-gamma and interleukin (IL)-2 producing cells, but a dramatic increase in tumor necrosis factor (TNF)-alpha secretion in animals receiving both monoclonal antibodies. These results suggest distinct roles for CD80 and CD86 in the initiation of EAE, resulting in the diverse clinical outcomes observed in this model of EAE.

Opposing effects of CTLA4-Ig and anti-CD80 (B7-1) plus anti-CD86 (B7-2) on experimental allergic encephalomyelitis.

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...; Pharmacology--PD; Encephalomyelitis, Allergic--Immunology--IM; Encephalomyelitis, Allergic--Prevention and Control--PC; Guinea Pigs; Immunization; Interferon Type II--Immunology--IM; Interferon Type II--Metabolism--ME; Interleukin-2--Immunology--IM; Interleukin-2 --Metabolism--ME; Mice; Mice, Inbred...

...Chemical Name: 4; (Immunosuppressive Agents; (Interleukin-2; (Membrane Glycoproteins; (Myelin Basic Proteins; (Tumor Necrosis Factor; (Pertussis Toxins; (Interferon Type II

15/3,K,AB/10 (Item 10 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08418271 95239129

CD28-B7 blockade after alloantigenic challenge in vivo inhibits Th1 cytokines but spares Th2.

Sayegh MH; Akalin E; Hancock WW; Russell ME; Carpenter CB; Linsley PS; Turka LA

Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

J Exp Med (UNITED STATES) May 1 1995, 181 (5) p1869-74, ISSN 0022-1007 Journal Code: I2V

Contract/Grant No.: RO1 AI-33100-03, AI, NIAID; R29 AI-349965-01, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Blocking the CD28-B7 T cell costimulatory pathway with the fusion protein **CTLA4Ig** inhibits alloimmune responses in vitro and in vivo and induces tolerance to cardiac allografts in mice and rats, but the mechanisms mediating the tolerant state in vivo are unknown. Here, we report the effects and potential mechanisms of **CTLA4Ig** in the rat renal allograft model. LEW rats were nephrectomized and received renal allografts from major histocompatibility complex-incompatible WF rats. While all untreated and control immunoglobulin (Ig)-treated animals acutely rejected their allografts and died, 86% of rats that received a single injection of **CTLA4Ig** on day 2 after transplantation had prolonged survival (> 60-100 days) with preserved renal function. By contrast, only 29% of animals that received **CTLA4Ig** on the day of engraftment had prolonged survival. Long-term survivors (> 100 days) exhibited donor-specific tolerance, accepting donor-matched WF but acutely rejecting third-party BN cardiac allografts. Immunohistological analysis of grafts sampled at 1 week after transplantation showed that both control and **CTLA4Ig**-treated animals had mononuclear cell infiltrates, with a higher percentage of CD4+ cells in the **CTLA4Ig**-treated group. However, while this was associated with vasculitis and tubulitis in control grafts, there was no evidence of tissue injury in **CTLA4Ig**-treated animals. The immune response leading to graft rejection in control animals was characterized by expression of the T helper (Th) type 1 cytokines interleukin (IL)-2 and interferon-gamma. In contrast, the persistent CD4+ infiltrate without graft rejection in **CTLA4Ig**-treated animals was associated with increased staining for the Th2-related cytokines IL-4 and IL-10. Furthermore, grafts from **CTLA4Ig**-treated animals had marked upregulation of intragraft staining for IgG1, but not IgG2a or IgG2b. Administration of rIL-2 to **CTLA4Ig**-treated animals restored allograft rejection in 50% of animals tested. These results confirm that blockade of the CD28-B7 pathway after alloantigenic challenge induces donor-specific acceptance of vascularized organ allografts, and indicates in this model that **CTLA4Ig** inhibits Th1 but spares Th2 cytokines in vivo.

Blocking the CD28-B7 T cell costimulatory pathway with the fusion protein **CTLA4Ig** inhibits alloimmune responses in vitro and in vivo and induces tolerance to cardiac allografts in...

... tolerant state in vivo are unknown. Here, we report the effects and potential mechanisms of **CTLA4Ig** in the rat renal allograft model. LEW rats were nephrectomized and received renal allografts from...

... acutely rejected their allografts and died, 86% of rats that received a

single injection of CTLA4Ig on day 2 after transplantation had prolonged survival (> 60-100 days) with preserved renal function. By contrast, only 29% of animals that received CTLA4Ig on the day of engraftment had prolonged survival. Long-term survivors (> 100 days) exhibited donor...

... Immunohistological analysis of grafts sampled at 1 week after transplantation showed that both control and CTLA4Ig-treated animals had mononuclear cell infiltrates, with a higher percentage of CD4+ cells in the CTLA4Ig -treated group. However, while this was associated with vasculitis and tubulitis in control grafts, there was no evidence of tissue injury in CTLA4Ig -treated animals. The immune response leading to graft rejection in control animals was characterized by expression of the T helper (Th) type 1 cytokines interleukin (IL)-2 and interferon-gamma . In contrast, the persistent CD4+ infiltrate without graft rejection in CTLA4Ig-treated animals was associated with increased staining for the Th2-related cytokines IL-4 and IL-10. Furthermore, grafts from CTLA4Ig -treated animals had marked upregulation of intragraft staining for IgG1, but not IgG2a or IgG2b. Administration of rIL-2 to CTLA4Ig-treated animals restored allograft rejection in 50% of animals tested. These results confirm that blockade...

... challenge induces donor-specific acceptance of vascularized organ allografts, and indicates in this model that CTLA4Ig inhibits Th1 but spares Th2 cytokines in vivo.

15/3, K, AB/11 (Item 11 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
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10/28/99

08165802 94275375

B7 and interleukin 12 cooperate for proliferation and interferon gamma production by mouse T helper clones that are unresponsive to B7 costimulation.

Murphy EE; Terres G; Macatonia SE; Hsieh CS; Mattson J; Lanier L; Wysocka M; Trinchieri G; Murphy K; O'Garra A
DNAX Research Institute, Palo Alto, California 94304-1104.

J Exp Med (UNITED STATES) Jul 1 1994, 180 (1) p223-31, ISSN 0022-1007
Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have previously shown that dendritic cells isolated after overnight culture, which can express B7 and are potent stimulators of naive T cell proliferation, are relatively poor at inducing the proliferation of a panel of murine T helper 1 (Th1) clones. Maximal stimulation of Th1 clones was achieved using unseparated splenic antigen presenting cells (APC). An explanation for these findings is provided in the present study where we show that FcR+ L cells transfected with B7 stimulate minimal proliferation of Th1 clones in response to anti-CD3 antibodies, in contrast to induction of significant proliferation of naive T cells. However, addition of interleukin 12 (IL-12) to cultures of Th1 cells stimulated with anti-CD3 and FcR+ B7 transfectants resulted in a very pronounced increase in proliferation and interferon gamma (IFN-gamma) production. Exogenous IL-12 did not affect the B7-induced proliferation of naive T cells. This showed that whereas costimulatory signals delivered via B7-CD28 interaction are sufficient to induce significant proliferation of naive T cells activated through occupancy of the T cell receptor, Th1 T cell clones require cooperative costimulation by B7 and IL-12. This costimulation was shown to be specific by inhibition of proliferation and IFN-gamma production using chimeric soluble cytolytic T lymphocyte-associated antigen 4-human IgG1Fc (CTLA4 -Ig) and anti-IL-12 antibodies. Furthermore, the significant antigen specific proliferation and IFN-gamma production by Th1 clones observed when splenocytes were used as APC was almost completely abrogated using

CTLA4 -Ig and anti-IL-12 antibodies. Thus two costimulatory signals, B7 and IL-12, account for the ability of splenic APC to induce maximal stimulation of Th1 clones. IL-10 downregulates the expression of IL-12 by IFN-gamma-stimulated macrophages and this may account largely for the ability of IL-10 to inhibit APC function of splenic and macrophage APC for the induction of Th1 cell proliferation and IFN-gamma production. Indeed we show that IL-12 can overcome the inhibitory effect of IL-10 for the APC-dependent induction of proliferation and IFN-gamma production by Th1 clones. These results suggest that proliferation by terminally differentiated Th1 clones, in contrast to naive T cells, requires stimulation via membrane-bound B7 and a cytokine, IL-12. It is possible that these signals may result in the activation of unresponsive T cells during an inflammatory response. IL-10, by its role in regulating such innate inflammatory responses, may thus help to maintain these T cells in an unresponsive state.

B7 and interleukin 12 cooperate for proliferation and **interferon gamma** production by mouse T helper clones that are unresponsive to B7 costimulation.

... Th1 cells stimulated with anti-CD3 and FcR+ B7 transfectants resulted in a very pronounced increase in proliferation and **interferon gamma** (IFN-gamma) production. Exogenous IL-12 did not affect the B7-induced proliferation of naive T cells...

... IL-12. This costimulation was shown to be specific by inhibition of proliferation and IFN-gamma production using chimeric soluble cytolytic T lymphocyte-associated antigen 4-human IgG1Fc (CTLA4-Ig) and anti-IL-12 antibodies. Furthermore, the significant antigen specific proliferation and IFN-gamma production by Th1 clones observed when splenocytes were used as APC was almost completely abrogated using **CTLA4** -Ig and anti-IL-12 antibodies. Thus two costimulatory signals, B7 and IL-12, account...

...maximal stimulation of Th1 clones. IL-10 downregulates the expression of IL-12 by IFN-gamma-stimulated macrophages and this may account largely for the ability of IL-10 to...

... function of splenic and macrophage APC for the induction of Th1 cell proliferation and IFN-gamma production. Indeed we show that IL-12 can overcome the inhibitory effect of IL-10 for the APC-dependent induction of proliferation and IFN-gamma production by Th1 clones. These results suggest that proliferation by terminally differentiated Th1 clones, in...

Descriptors: Antigens, CD80--Physiology--PH; *Interferon Type II--Biosynthesis--BI; *Interleukins--Physiology--PH; *Lymphocyte Transformation; *T-Lymphocytes, Helper-Inducer--Physiology--PH

Chemical Name: Antigens, CD80; (Antigens, Differentiation; (CTLA-4; (Interleukin-12; (Interleukins; (Interleukin-10; (Interferon Type II

15/3,K,AB/12 (Item 12 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08164469 94246161

Regulation of immunostimulatory function and costimulatory molecule (B7-1 and B7-2) expression on murine dendritic cells.

Larsen CP; Ritchie SC; Hendrix R; Linsley PS; Hathcock KS; Hodes RJ; Lowry RP; Pearson TC

Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322.

J Immunol (UNITED STATES) Jun 1 1994, 152 (11) p5208-19, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: 1R29-AI33588-01A1, AI, NIAID; R01-AI30322, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Dendritic cells (DC) play a critical role in the initiation of T cell-mediated immune responses, and express costimulatory molecules that are required for optimal activation of unprimed T cells. Studies on the regulation of the costimulatory molecules on DC have produced evidence from several systems that GM-CSF can up-regulate expression of **CTLA4** counter receptor (**CTLA4-CR**) (but not intercellular adhesion molecule 1 (ICAM-1) and heat stable Ag (HsAg)) on DC. This is demonstrated on splenic DC, Langerhans cells, kidney DC in culture, and in a skin-explant culture system, in which the increased expression of **CTLA4-CR** on Langerhans cells (LC) occurs concomitantly with their migration out of skin. Interestingly, despite the ability of both GM-CSF and IFN-gamma to increase **CTLA4**-CR and maintain similar levels of ICAM-1, HsAg, and MHC molecule expression, the functional consequences of these cytokines on splenic DC are distinctly different. GM-CSF enhances the ability of DC to stimulate both T cell proliferation and cytokine release, whereas IFN-gamma causes no increase in immunostimulatory function. Further analysis of the **CTLA4-CR** on these cell populations by using the GL-1 and IG10 mAbs has shown that GM-CSF-cultured DC express high levels of both B7-1 and B7-2, whereas IFN-gamma-cultured DC express increased levels of only B7-2. These results suggest that optimal stimulation of unprimed T cells to proliferate and release cytokines may require participation of both of these **CTLA4** counter receptors, and confirm the importance of GM-CSF for the maturation of DC into potent stimulators of T cell activation.

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... cells, kidney DC in culture, and in a skin-explant culture system, in which the increased expression of **CTLA4-CR** on Langerhans cells (LC) occurs concomitantly with their migration out of skin. Interestingly, despite the ability of both GM-CSF and IFN-gamma to increase **CTLA4**-CR and maintain similar levels of ICAM-1, HsAg, and MHC molecule expression, the functional...

... the ability of DC to stimulate both T cell proliferation and cytokine release, whereas IFN-gamma causes no increase in immunostimulatory function. Further analysis of the **CTLA4-CR** on these cell populations by using the GL-1 and IG10 mAbs has shown...

...CSF-cultured DC express high levels of both B7-1 and B7-2, whereas IFN-gamma-cultured DC express increased levels of only B7-2. These results suggest that optimal stimulation of unprimed T cells to proliferate and release cytokines may require participation of both of these **CTLA4** counter receptors, and confirm the importance of GM-CSF for the maturation of DC into...

...; Cells--Drug Effects--DE; Dendritic Cells--Immunology--IM; Granulocyte-Macrophage Colony-Stimulating Factor--Pharmacology--PD; Interferon Type II--Pharmacology--PD; Langerhans Cells--Physiology --PH; Lymphocyte Transformation; Mice; Mice, Inbred C3H; Mice... Chemical Name: Antigens, CD80; (Antigens, Differentiation; (B7-2 protein; (CTLA-4; (Interferon Type II; (Granulocyte-Macrophage Colony-Stimulating Factor

? ds

Set	Items	Description
S1	833	CTLA4?
S2	14115	GAMMA(W) INTERFERON
S3	6	S1 AND S2
S4	6	RD (unique items)
S5	114256	COMPLEMENT
S6	4	S1 AND S5
S7	3	RD (unique items)
S8	114337	INTERFERON
S9	79	S1 AND S8
S10	285654	GAMMA
S11	74	S9 AND S10
S12	68	S11 NOT S3
S13	1944665	INCREAS?
S14	20	S12 AND S13
S15	12	RD (unique items)
? s macrophage		
	S16	101877 MACROPHAGE
? s s1 and s16		
	833	S1
	101877	S16
	S17	40 S1 AND S16
? rd		
	...completed examining records	
	S18	29 RD (unique items)
? s inhibit?		
	S19	1310311 INHIBIT?
? s s18 and s19		
	29	S18
	1310311	S19
	S20	13 S18 AND S19
? t s20/3,k,ab/1-13		

20/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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09189262 97426482
The role of the B7 costimulatory pathway in experimental cold ischemia/reperfusion injury.

Takada M; Chandraker A; Nadeau KC; Sayegh MH; Tilney NL
Department of Surgery, Brigham and Women's Hospital, Boston,
Massachusetts 02115, USA.

J Clin Invest (UNITED STATES) Sep 1 1997, 100 (5) p1199-203, ISSN
0021-9738 Journal Code: HS7
Contract/Grant No.: 9 R01 DK 46190-23, DK, NIDDK; P01 AI 40152-01, AI,
NIAID

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Ischemia/reperfusion injury associated with organ retrieval and storage influences the development of chronic graft dysfunction, the major clinical problem in solid organ transplantation. The potential role of mononuclear cells (T cells and monocyte/macrophages) in this type of injury is unknown. Inbred male Lewis rats were uninephrectomized and the left kidney perfused in situ with 10 ml of iced University of Wisconsin solution. Immunohistological studies showed mononuclear cell infiltration of the ischemic organs associated with the upregulation of MHC class II antigen

expression. Reverse transcriptase-PCR indicated that T cell associated cytokines and monocyte/macrophage activation markers/products are upregulated early after the ischemic insult. B7 expression occurred within 24 h and peaked at 3 d. Plasma creatinine levels rose transiently with complete recovery of renal function by 5 d. Animals began to develop progressive proteinuria after 8-12 wk, indicative of the long-term functional consequences of early ischemia/reperfusion injury. Blockade of T cell CD28-B7 costimulation with CTLA4Ig resulted in significant inhibition of T cell and macrophage infiltration and activation in situ. Treated animals did not exhibit transient renal dysfunction, nor developed proteinuria over time. This is the first demonstration that blocking T cell costimulatory activation in the absence of alloantigen can prevent the early and late consequences of ischemia/reperfusion injury.

... class II antigen expression. Reverse transcriptase-PCR indicated that T cell associated cytokines and monocyte/macrophage activation markers/products are upregulated early after the ischemic insult. B7 expression occurred within 24...

... functional consequences of early ischemia/reperfusion injury. Blockade of T cell CD28-B7 costimulation with CTLA4Ig resulted in significant inhibition of T cell and macrophage infiltration and activation in situ. Treated animals did not exhibit transient renal dysfunction, nor developed...

20/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)
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09186729 97427050

Enhanced immune costimulatory activity of primary acute myeloid leukaemia blasts after retrovirus-mediated gene transfer of B7.1.

Hirst WJ; Buggins A; Darling D; Gaken J; Farzaneh F; Mufti GJ
Departments of Haematological Medicine and Molecular, King's College School of Medicine and Dentistry, London, UK.

Gene Ther (ENGLAND) Jul 1997, 4 (7) p691-9, ISSN 0969-7128

Journal Code: CCE

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Gene modification of malignant cells to express immune stimulators (cytokines and immune costimulators) has provided the basis for a novel form of immunotherapy. Using a MPSV-based retroviral vector with hygromycin resistance gene as a selectable marker, we have studied retrovirus-mediated gene transfer of an immune costimulator, B7.1, into primary human acute myeloid leukaemia (AML) cells and the subsequent induction of immune costimulatory function. AML blasts from 10 patients were transduced by co-culture for 48 h with or without haemopoietic growth factors (HGFs). In the absence of HGFs, transduction efficiency (TE), as judged by % B7.1 expressing cells, was low, varying from 0.3 to 8.2% (median 1.5%). Addition of HGFs increased the median TE 1.8-fold with stem cell factor alone and 2.6-fold with SCF, interleukin-3 and GM-CSF. Effects on cell cycling alone could not explain this difference, suggesting other factors such as virus binding and promoter activity, are also involved. CFU-AL assays indicated a higher transduction efficiency of clonogenic cells, which was not improved by growth factors. Limited duration of cell growth prevented significant expansion of transduced populations by culture in the presence of hygromycin. Although not increasing transduction efficiency, CD34 enrichment enhanced drug selection, by targeting cells with the greatest self-renewal capacity. Immunoselection of B7.1 expressing cells produced transduced populations with 30-60% expressing B7.1. In an allogeneic mixed leukaemic cell/T lymphocyte reaction (MLLR) transduced AML cells enriched by immunoselection were able to stimulate allogeneic T cells (CD4 and CD8 positive), which could be inhibited by a solubilised B7 receptor, CTLA4 Ig. Our results demonstrate that using a replication

incompetent retroviral vector, it is possible to introduce the immune costimulator B7.1 into primary AML-blasts and by immunoselection, enrich the transduced cells, which may be used for subsequent administration as an autologous cellular vaccine.

...immunoselection were able to stimulate allogeneic T cells (CD4 and CD8 positive), which could be inhibited by a solubilised B7 receptor, CTLA4 .Ig. Our results demonstrate that using a replication incompetent retroviral vector, it is possible to...

; Coculture; Combined Modality Therapy; Granulocyte-Macrophage Colony-Stimulating Factor--Therapeutic Use--TU; Immunotherapy; Interleukin-3--Therapeutic Use--TU; Leukemia, Myeloid--Immunology...

Chemical Name: Antigens, CD80; (Genetic Vectors; (Interleukin-3; (Stem Cell Factor; (Granulocyte-Macrophage Colony-Stimulating Factor

20/3,K,AB/3 (Item 3 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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09102140 97347911

Steroids inhibit uptake and/or processing but not presentation of antigen by airway dendritic cells.

Holt PG; Thomas JA

Institute for Child Health Research, West Perth, Australia.

Immunology (ENGLAND) May 1997, 91 (1) p145-50, ISSN 0019-2805
Journal Code: GH7

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Recent studies from our laboratory indicate that local and (particularly) systemic steroids can modulate the traffic of dendritic cells (DC) through resting and inflamed airway epithelial tissues. The present report focuses upon the T-cell activating properties of DC, which are controlled by granulocyte-macrophage colony-stimulating factor (GM-CSF) signals, and in particular the question of whether the DC-stimulating effects of GM-CSF are susceptible to regulation by steroids. We present evidence that while dexamethasone inhibited GM-CSF-dependent uptake and/or processing of exogenous antigen by DC, it was ineffective in blocking the presentation of preprocessed self antigen to alloreactive T cells in a one-way mixed lymphocyte reaction (MLR). Associated GM-CSF-induced up-regulation of major histocompatibility complex (MHC) class II and CTLA4 ligand expression by DC were also unaffected by dexamethasone phosphate (DX), reinforcing the view that the inhibitory effects of steroids on the T-cell activating functions of DC are restricted to steps upstream from presentation of processed antigen to the T-cell receptor (TCR). These findings have potentially important implications in relation to the use of topical steroids in the treatment of atopic asthma, a disease in which local T-cell activation in airway tissue is a key pathogenic factor, and which furthermore is characterized by intense production of GM-CSF within the airway epithelium.

Steroids inhibit uptake and/or processing but not presentation of antigen by airway dendritic cells.

... report focuses upon the T-cell activating properties of DC, which are controlled by granulocyte-macrophage colony-stimulating factor (GM-CSF) signals, and in particular the question of whether the DC...

...of GM-CSF are susceptible to regulation by steroids. We present evidence that while dexamethasone inhibited GM-CSF-dependent uptake and/or processing of exogenous antigen by DC, it was ineffective...

... MLR). Associated GM-CSF-induced up-regulation of major histocompatibility complex (MHC) class II and CTLA4 ligand expression by DC were also unaffected by dexamethasone phosphate (DX), reinforcing the view that the inhibitory effects of steroids on the T-cell activating

functions of DC are restricted to steps...
...; Presentation--Drug Effects--DE; Antigens, Differentiation
--Immunology--IM; Cell Culture; Dendritic Cells--Immunology--IM;
Granulocyte Macrophage Colony-Stimulating Factors, Recombinant
--Antagonists and Inhibitors--AI; Granulocyte Macrophage
Colony-Stimulating Factors, Recombinant--Immunology--IM; Histocompatibility Antigens Class II--Immunology--IM; Lymphocyte Culture Test...
Chemical Name: Antigens, Differentiation; (CTLA-4; (Glucocorticoids, Synthetic; (Granulocyte Macrophage Colony-Stimulating Factors, Recombinant; (Histocompatibility Antigens Class II; (Dexamethasone; (Ovalbumin

20/3, K, AB/4 (Item 4 from file: 155)

DIALOG(R) File 155: MEDLINE(R)

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10/30/99

08932922 97144626

CD28-B7 T cell costimulatory blockade by CTLA4Ig in the rat renal allograft model: inhibition of cell-mediated and humoral immune responses in vivo.

Akalin E; Chandraker A; Russell ME; Turka LA; Hancock WW; Sayegh MH
Laboratory of Immunogenetics and Transplantation, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.
Transplantation (UNITED STATES) Dec 27 1996, 62 (12) p1942-5, ISSN 0041-1337 Journal Code: WEJ

Contract/Grant No.: AI33100, AI, NIAID; AI37691, AI, NIAID; AI349965, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Blocking CD28-B7 T-cell costimulation by CTLA4Ig induces tolerance to rat renal allografts and inhibits Th1, but spares Th2, cytokines. We now report on the mechanisms of CD28-B7 blockade in this model. Lymphocytes from CTLA4Ig-treated animals showed significant reduction of mixed lymphocyte response, as well as antidonor cytotoxic T-cell effector function, as compared with rejecting controls. Flow cytometry studies on sera of renal allograft recipients showed complete inhibition of antidonor humoral responses by CTLA4Ig. Analysis by reverse transcriptase-polymerase chain reaction and immunohistology showed that intragraft macrophage products, monocyte chemoattractant protein-1 and inducible nitric oxide synthase, were reduced by CTLA4Ig therapy. Immunohistologic studies also showed reduced intragraft macrophage infiltration and decreased staining for the fibrogenic and mitogenic growth factor, transforming-growth-factor-beta. These results indicate that CD28-B7 blockade inhibits cell-mediated and humoral immune responses, and suggest that strategies targeting T-cell costimulation may provide a novel approach to prevent chronic allograft rejection.

CD28-B7 T cell costimulatory blockade by CTLA4Ig in the rat renal allograft model: inhibition of cell-mediated and humoral immune responses in vivo.

Blocking CD28-B7 T-cell costimulation by CTLA4Ig induces tolerance to rat renal allografts and inhibits Th1, but spares Th2, cytokines. We now report on the mechanisms of CD28-B7 blockade in this model. Lymphocytes from CTLA4Ig-treated animals showed significant reduction of mixed lymphocyte response, as well as antidonor cytotoxic T...

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infiltration and decreased staining for the fibrogenic and mitogenic growth factor, transforming growth factor-beta. These results indicate that CD28-B7 blockade inhibits cell-mediated and humoral immune responses, and suggest that strategies targeting T-cell costimulation may...

20/3,K,AB/5 (Item 5 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08670052 96188769

In vitro characterization of rat bone marrow-derived dendritic cells and their precursors.

Chen-Woan M; Delaney CP; Fournier V; Wakizaka Y; Murase N; Fung J; Starzl TE; Demetris AJ

Pittsburgh Transplantation Institute, University of Pittsburgh Health Science Center, PA 15261, USA.

J Leukoc Biol (UNITED STATES) Feb 1996, 59 (2) p196-207, ISSN 0741-5400 Journal Code: IWY

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Although the rat is commonly used for basic immunology and transplantation research, phenotypic and functional characterization of rat dendritic cells (DCs) lags behind similar studies in the human and mouse. Therefore, these features were examined using DCs propagated from cultures of rat bone marrow maintained in a medium supplemented with granulocyte-monocyte colony-stimulating factor. Analysis of cytopsin preparations of cultured cells showed that DCs arise from OX7+ myelomonocytic precursors. Typical mature rat DCs were morphologically similar to their mouse and human counterparts and expressed major histocompatibility complex (MHC) class II (common part determinant of Ia), OX62 (integrin molecule), OX7 (CD90), ICAM-1 (CD54), and CTLA4 counterreceptor, but were negative for OX8 (CD8), OX19 (CD5), W3/25 (CD4), and ED2, a rat macrophage marker. Functional analysis of OX62+ sorted DCs showed that they could effectively present the soluble antigen ovalbumin to naive T cells in vitro. A combination of anti-MHC class II monoclonal antibody and CTLA4-immunoglobulin inhibited allostimulatory ability more effectively than either reagent alone. Implications for studying the role of DCs in immune responses in the rat are discussed.

... II (common part determinant of Ia), OX62 (integrin molecule), OX7 (CD90), ICAM-1 (CD54), and CTLA4 counterreceptor, but were negative for OX8 (CD8), OX19 (CD5), W3/25 (CD4), and ED2, a rat macrophage marker. Functional analysis of OX62+ sorted DCs showed that they could effectively present the soluble...

... naive T cells in vitro. A combination of anti-MHC class II monoclonal antibody and CTLA4-immunoglobulin inhibited allostimulatory ability more effectively than either reagent alone. Implications for studying the role of DCs...

20/3,K,AB/6 (Item 6 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08172941 95053714

B70/B7-2 is identical to CD86 and is the major functional ligand for CD28 expressed on human dendritic cells.

Caux C; Vanbervliet B; Massacrier C; Azuma M; Okumura K; Lanier LL; Banchereau J

Laboratory for Immunological Research, Schering-Plough, Dardilly, France.

J Exp Med (UNITED STATES) Nov 1 1994, 180 (5) p1841-7, ISSN 0022-1007
Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Dendritic cells comprise a system of highly efficient antigen-presenting cells involved in the initiation of T cell responses. Herein, we investigated the role of the CD28 pathway during alloreactive T cell proliferation induced by dendritic-Langerhans cells (D-Lc) generated by culturing human cord blood CD34+ progenitor cells with granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha. In addition to expressing CD80 (B7/BB1), a subset of D-Lc expressed B70/B7-2. Binding of the CTLA4-Ig fusion protein was completely inhibited by a combination of monoclonal antibodies (mAbs) against CD80 and B70/B7-2, indicating the absence of expression of a third ligand for CD28/CTLA-4. It is interesting to note that mAbs against CD86 completely prevented the binding of CTLA4-Ig in the presence of mAbs against CD80 and bound to a B70/B7-2-transfected fibroblast cell line, demonstrating that the B70/B7-2 antigen is identical to CD86. CD28 triggering was essential during D-Lc-induced alloreaction as it was inhibited by mAbs against CD28 (9 out of 11 tested). However, none of six anti-CD80 mAbs demonstrated any activity on the D-Lc-induced alloreaction, though some were previously described as inhibitory in assays using CD80-transfected cell lines. In contrast, a mAb against CD86 (IT-2) was found to suppress the D-Lc-dependent alloreaction by 70%. This inhibitory effect was enhanced to > or = 90% when a combination of anti-CD80 and anti-CD86 mAbs was used. The present results demonstrate that D-Lc express, in addition to CD80, the other ligand for CTLA-4, CD86 (B70/B7-2), which plays a primordial role during D-Lc-induced alloreaction.

... Langerhans cells (D-Lc) generated by culturing human cord blood CD34+ progenitor cells with granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha. In addition to expressing CD80 (B7/BB1), a subset of D-Lc expressed B70/B7-2. Binding of the CTLA4-Ig fusion protein was completely inhibited by a combination of monoclonal antibodies (mAbs) against CD80 and B70/B7-2, indicating the...

...4. It is interesting to note that mAbs against CD86 completely prevented the binding of CTLA4 -Ig in the presence of mAbs against CD80 and bound to a B70/B7-2...

... identical to CD86. CD28 triggering was essential during D-Lc-induced alloreaction as it was inhibited by mAbs against CD28 (9 out of 11 tested). However, none of six anti-CD80...

... demonstrated any activity on the D-Lc-induced alloreaction, though some were previously described as inhibitory in assays using CD80-transfected cell lines. In contrast, a mAb against CD86 (IT-2) was found to suppress the D-Lc-dependent alloreaction by 70%. This inhibitory effect was enhanced to > or = 90% when a combination of anti-CD80 and anti-CD86...

20/3,K,AB/7 (Item 7 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08167962 94321918

Comparative analysis of B7-1 and B7-2 costimulatory ligands: expression and function.

Hathcock KS; Laszlo G; Pucillo C; Linsley P; Hodes RJ

Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

J Exp Med (UNITED STATES) Aug 1 1994, 180 (2) p631-40, ISSN 0022-1007
Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Antigen-specific T cell activation requires the engagement of the T cell

receptor (TCR) with antigen as well as the engagement of appropriate costimulatory molecules. The most extensively characterized pathway of costimulation has been that involving the interaction of CD28 and CTLA4 on the T cell with B7 (now termed B7-1) on antigen presenting cells. Recently, B7-2 a second costimulatory ligand for CTLA4, was described, demonstrating the potential complexity of costimulatory interactions. This report examines and compares the expression and function of B7-1 and B7-2. Overall these results indicate that (a) B7-1 and B7-2 can be expressed by multiple cell types, including B cells, T cells, macrophages, and dendritic cells, all of which are therefore candidate populations for delivering costimulatory signals mediated by these molecules; (b) stimulating B cells with either LPS or anti-IgD-dextran induced expression of both B7-1 and B7-2, and peak expression of both costimulatory molecules occurred after 18-42 h of culture. Expression of B7-2 on these B cell populations was significantly higher than expression of B7-1 at all times assayed after stimulation; (c) blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production, without affecting early consequences of TCR signaling such as induction of CD69 or interleukin 2 receptor alpha (IL-2R alpha); and (d) expression of B7-1 and of B7-2 can be regulated by a variety of stimuli. Moreover, expression of B7-1 and B7-2 can be independently regulated by the same stimulus, providing an additional complexity in the mechanisms available for regulating costimulation and hence immune response.

... most extensively characterized pathway of costimulation has been that involving the interaction of CD28 and CTLA4 on the T cell with B7 (now termed B7-1) on antigen presenting cells. Recently, B7-2 a second costimulatory ligand for CTLA4, was described, demonstrating the potential complexity of costimulatory interactions. This report examines and compares the...

... B7-1 at all times assayed after stimulation; (c) blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production, without affecting early consequences of TCR signaling...

...; IM; Base Sequence; Cells, Cultured; Cytokines--Biosynthesis--BI; CHO Cells; DNA; Hamsters; Ligands; Lymphocyte Transformation; Macrophage Activation; Macrophages--Immunology--IM; Mice; Mice, Inbred Strains; Molecular Sequence Data; Rabbits; Receptors, Interleukin-2...

20/3,K,AB/8 (Item 8 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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08165802 94275375

B7 and interleukin 12 cooperate for proliferation and interferon gamma production by mouse T helper clones that are unresponsive to B7 costimulation.

Murphy EE; Terres G; Macatonia SE; Hsieh CS; Mattson J; Lanier L; Wysocka M; Trinchieri G; Murphy K; O'Garra A

DNAX Research Institute, Palo Alto, California 94304-1104.

J Exp Med (UNITED STATES) Jul 1 1994, 180 (1) p223-31, ISSN 0022-1007

Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have previously shown that dendritic cells isolated after overnight culture, which can express B7 and are potent stimulators of naive T cell proliferation, are relatively poor at inducing the proliferation of a panel of murine T helper 1 (Th1) clones. Maximal stimulation of Th1 clones was achieved using unseparated splenic antigen presenting cells (APC). An explanation for these findings is provided in the present study where we show that FcR⁺ L cells transfected with B7 stimulate minimal proliferation of Th1 clones in response to anti-CD3 antibodies, in contrast to induction of significant proliferation of naive T cells. However, addition of

interleukin 12 (IL-12) to cultures of Th1 cells stimulated with anti-CD3 and FcR+ B7 transfectants resulted in a very pronounced increase in proliferation and interferon gamma (IFN-gamma) production. Exogenous IL-12 did not affect the B7-induced proliferation of naive T cells. This showed that whereas costimulatory signals delivered via B7-CD28 interaction are sufficient to induce significant proliferation of naive T cells activated through occupancy of the T cell receptor, Th1 T cell clones require cooperative costimulation by B7 and IL-12. This costimulation was shown to be specific by inhibition of proliferation and IFN-gamma production using chimeric soluble cytolytic T lymphocyte-associated antigen 4-human IgG1Fc (CTLA4-Ig) and anti-IL-12 antibodies. Furthermore, the significant antigen specific proliferation and IFN-gamma production by Th1 clones observed when splenocytes were used as APC was almost completely abrogated using CTLA4-Ig and anti-IL-12 antibodies. Thus two costimulatory signals, B7 and IL-12, account for the ability of splenic APC to induce maximal stimulation of Th1 clones. IL-10 downregulates the expression of IL-12 by IFN-gamma-stimulated macrophages and this may account largely for the ability of IL-10 to inhibit APC function of splenic and macrophage APC for the induction of Th1 cell proliferation and IFN-gamma production. Indeed we show that IL-12 can overcome the inhibitory effect of IL-10 for the APC-dependent induction of proliferation and IFN-gamma production by Th1 clones. These results suggest that proliferation by terminally differentiated Th1 clones, in contrast to naive T cells, requires stimulation via membrane-bound B7 and a cytokine, IL-12. It is possible that these signals may result in the activation of unresponsive T cells during an inflammatory response. IL-10, by its role in regulating such innate inflammatory responses, may thus help to maintain these T cells in an unresponsive state.

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... by Th1 clones observed when splenocytes were used as APC was almost completely abrogated using CTLA4-Ig and anti-IL-12 antibodies. Thus two costimulatory signals, B7 and IL-12, account...

...stimulated macrophages and this may account largely for the ability of IL-10 to inhibit APC function of splenic and macrophage APC for the induction of Th1 cell proliferation and IFN-gamma production. Indeed we show that IL-12 can overcome the inhibitory effect of IL-10 for the APC-dependent induction of proliferation and IFN-gamma production...

20/3, K, AB/9 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)
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11538085 BIOSIS NO.: 199800319417
Costimulatory pathways in lymphocyte proliferation induced by the simian immunodeficiency virus SIVsmmPBj14.

AUTHOR: Whetter Linda; Novembre Francis J; Saucier Michelle; Gummuluru Suryaram; Dewhurst Stephen(a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Univ. Rochester Med. Cent.,
Rochester, NY 14642, USA

JOURNAL: Journal of Virology 72 (7):p6155-6158 July, 1998

ISSN: 0022-538X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The PBj14 isolate of the simian immunodeficiency virus SIV_{smm}PBj14 is unique among primate lentiviruses in its ability to induce lymphocyte proliferation and acutely lethal disease. The studies reported here show that viral induction of T-cell proliferation requires accessory cells, such as primary monocytes or Raji B-lymphoma cells, as well as the presence of a putative immunoreceptor tyrosine-based activation motif within the viral Nef protein. Addition of CTLA4-immunoglobulin fusion protein or anti-B7 antibodies to virally infected T cells led to substantial, but not complete, inhibition of monocyte-costimulated T-cell proliferation-suggesting that both CD28/B7-dependent and non-CD28-dependent pathways may contribute to the costimulation of virally induced lymphoproliferation. Finally, cyclosporin A, a specific inhibitor of the calcium-calmodulin-regulated phosphatase activity of calcineurin, which influences activation of the transcription factor nuclear factor of activated T cells, was shown to block virally mediated T-cell proliferation. Taken together, these findings suggest that the effect of SIV_{smm}PBj14 on T-cell activation may be functionally analogous, at least in part, to the effect of engagement of the T-cell receptor.

...**ABSTRACT:** of a putative immunoreceptor tyrosine-based activation motif within the viral Nef protein. Addition of CTLA4-immunoglobulin fusion protein or anti-B7 antibodies to virally infected T cells led to substantial, but not complete, inhibition of monocyte-costimulated T-cell proliferation-suggesting that both CD28/B7-dependent and non-CD28
...

...pathways may contribute to the costimulation of virally induced lymphoproliferation. Finally, cyclosporin A, a specific inhibitor of the calcium-calmodulin-regulated phosphatase activity of calcineurin, which influences activation of the transcription...

DESCRIPTORS:

ORGANISMS: PARTS ETC: macrophage--

20/3,K,AB/10 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)
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10758714 BIOSIS NO.: 199799379859
CD28-B7 T cell costimulatory blockage by CTLA4Ig in the rat renal allograft model: Inhibition of cell-mediated and humoral immune responses in vivo.

AUTHOR: Akkalin Enver; Chandraker Anil; Russell Mary E; Turka Laurence A; Hancock Wayne W; Sayegh Mohamed H(a)
AUTHOR ADDRESS: (a)Lab. Immunogenetics Transplantation, Brigham Women's Hosp., 75 Francis St., Boston, MA 02115, USA

JOURNAL: Transplantation (Baltimore) 62 (12):p1942-1945 1996
ISSN: 0041-1337
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Blocking CD28-B7 T-cell costimulation by CTLA4Ig induces tolerance to rat renal allografts and inhibits Th1, but spares Th2, cytokines. We now report on the mechanisms of CD28-B7 blockade in this model. Lymphocytes from CTLA4Ig-treated animals showed significant reduction of mixed lymphocyte response, as well as antidonor cytotoxic T-cell effector function, as compared with rejecting controls. Flow cytometry studies on sera of renal allograft recipients showed complete inhibition of antidonor humoral responses by CTLA4Ig. Analysis by reverse transcriptase-polymerase chain reaction and immunohistology showed that intragraft macrophage products, monocyte chemoattractant protein-1 and inducible nitric oxide synthase, were reduced by CTLA4Ig therapy. Immunohistologic studies also

showed reduced intragraft macrophage infiltration and decreased staining for the fibrogenic and mitogenic growth factor, transforming growth factor-beta. These results indicate that CD28-B7 blockade inhibits cell-mediated and humoral immune responses, and suggest that strategies targeting T-cell costimulation may provide a novel approach to prevent chronic allograft rejection.

CD28-B7 T cell costimulatory blockage by CTLA4Ig in the rat renal allograft model: Inhibition of cell-mediated and humoral immune responses in vivo.

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MISCELLANEOUS TERMS: ...CTLA4 IMMUNOGLOBULIN...

...CTLA4IG; ...

...MACROPHAGE;

20/3,K,AB/11 (Item 3 from file: 55)
DIALOG(R) File 55:Biosis Preiviews(R)
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10124494 BIOSIS NO.: 199698579412
Mechanisms of tolerance to renal allografts by CTLA4Ig:
Inhibition of cellular immunity, humoral immunity, and
macrophage activation in vivo.

AUTHOR: Akalin E; Turka L A; Hancock W W; Russell M E; Chandraker A;
Willett T; Carpenter C B; Sayegh M H
AUTHOR ADDRESS: Renal Div., Brigham and Women's Hosp., Harvard Sch. Public
Health, Boston, MA, USA

JOURNAL: Journal of the American Society of Nephrology 6 (3):p1053 1995

CONFERENCE/MEETING: Annual Meeting of the American Society of Nephrology
San Diego, California, USA November 5-8, 1995

ISSN: 1046-6673

RECORD TYPE: Citation

LANGUAGE: English

Mechanisms of tolerance to renal allografts by CTLA4Ig:
Inhibition of cellular immunity, humoral immunity, and
macrophage activation in vivo.

20/3,K,AB/12 (Item 4 from file: 55)

09414982 BIOSIS NO.: 199497423352
The Effect of Combination Cyclosporine and CTLA4-Ig Therapy on
Cardiac Allograft Survival.

AUTHOR: Bolling Steven F(a); Lin Hau; Wei Ru-Qi; Linsley Peter; Turka
Laurence A

AUTHOR ADDRESS: (a)Univ. Michigan Hosp., Sect. Thoracic Surg., 2120D
Taubman Cent., Box 0344, 1500 E. Medical Cente, USA

JOURNAL: Journal of Surgical Research 57 (1):p60-64 1994

ISSN: 0022-4804

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Transplant rejection requires not only T cell receptor/CD3 complex activation by foreign MHC, but also additional costimulatory signals, as T cell receptor activation alone is insufficient for induction of the immune response. The CD28 receptor on helper T cells, interacting with its ligand B7 on activated B cells or macrophages, provides this costimulus to support T cell activity. **CTLA4Ig** (a soluble CD28 receptor analog), binds B7 and **inhibits** CD28 activation. As cyclosporine (CsA) has many side effects and **CTLA4Ig** alone has a significant benefit upon cardiac allograft survival, we theorized that allograft survival could be improved by using **CTLA4Ig** with lowered dose CsA. In vitro, high-dose **CTLA4Ig** inhibited the mixed lymphocyte culture reaction (MLR) between MHC-incompatible rat strains. Furthermore, there was synergistic suppression of MLR by low-dose **CTLA4Ig** combined with low-dose CsA. In vivo studies used a cervical heterotopic transplant model. Control recipients received no immunotherapy. Experimental recipients received low-dose CsA (1.5 mg/kg/day im) times 14 days after transplant or **CTLA4Ig** (10, 50, or 150 mu-g IP times 7 days). Combination animals received both **CTLA4Ig** and CsA. These studies showed that low doses of CsA and **CTLA4Ig** were additive in vivo, although no additional benefit was seen when CsA was combined with high-dose **CTLA4Ig**. These data suggest that the combination of low-dose CsA plus **CTLA4Ig** may prove useful in clinical transplantation to maximize immunosuppression and minimize side effects.

The Effect of Combination Cyclosporine and CTLA4-Ig Therapy on
Cardiac Allograft Survival.

...**ABSTRACT:** B7 on activated B cells or macrophages, provides this costimulus to support T cell activity. **CTLA4Ig** (a soluble CD28 receptor analog), binds B7 and **inhibits** CD28 activation. As cyclosporine (CsA) has many side effects and **CTLA4Ig** alone has a significant benefit upon cardiac allograft survival, we theorized that allograft survival could be improved by using **CTLA4Ig** with lowered dose CsA. In vitro, high-dose **CTLA4Ig** inhibited the mixed lymphocyte culture reaction (MLR) between MHC-incompatible rat strains. Furthermore, there was synergistic suppression of MLR by low-dose **CTLA4Ig** combined with low-dose CsA. In vivo studies used a cervical heterotopic transplant model. Control...

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MISCELLANEOUS TERMS: ...CTLA4 IMMUNOGLOBULIN...
...MACROPHAGE;

20/3,K,AB/13 (Item 5 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)
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09023106 BIOSIS NO.: 199497031476
B70 antigen is a second ligand for CTLA-4 and CD28.

AUTHOR: Azuma Miyuki(a); Ito Daisuke; Yagita Hideo(a); Okumura Ko(a);
Phillips Joseph H; Lanier Lewis L; Somoza Chamorro
AUTHOR ADDRESS: (a)Dep. Immunol., Juntendo Univ. Sch. Med., Hongo 2-1-1,
Bunkyo-ku, Tokyo 113, Japan

JOURNAL: Nature (London) 366 (6450):p76-79 1993
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The membrane antigen B7/BB1 (refs 1, 2) is expressed on activated B cells, macrophages and dendritic cells, and binds to a counter-receptor, CD28, expressed on T lymphocytes and thymocytes. Interaction between CD28 and B7 results in potent costimulation of T-cell activation initiated through the CD3/T-cell receptor complex. Discrepancies between results with anti-CD28 and anti-B7 antibodies have suggested the existence of a second ligand for CD28 and CTLA-4 (refs 3, 6-8). We have generated a monoclonal antibody, IT2, that reacts with a 70K glycoprotein (B70). B70 complementary DNA was cloned from a B-lymphoblastoid cell line library and encodes a new protein of the immunoglobulin superfamily with limited homology to B7. B70 is expressed on resting monocytes and dendritic cells and on activated, but not resting, T, NK and B lymphocytes. IT2 substantially inhibited the binding of a CTLA4-immunoglobulin fusion protein to human B-lymphoblastoid cell lines and, together with anti-B7 antibody, completely blocked CTLA-4 binding. Further IT2 efficiently inhibited primary allogeneic mixed lymphocyte responses. These findings indicate that B70 is a second ligand for CD28 and CTLA-4 and may play an important role for costimulation of T cells in a primary immune response.

...**ABSTRACT:** dendritic cells and on activated, but not resting, T, NK and B lymphocytes. IT2 substantially inhibited the binding of a CTLA4-immunoglobulin fusion protein to human B-lymphoblastoid cell lines and, together with anti-B7 antibody, completely blocked CTLA-4 binding. Further IT2 efficiently inhibited primary allogeneic mixed lymphocyte responses. These findings indicate that B70 is a second ligand for...

MISCELLANEOUS TERMS: ...MACROPHAGE;
? ds

Set	Items	Description
S1	833	CTLA4?
S2	14115	GAMMA(W)INTERFERON
S3	6	S1 AND S2
S4	6	RD (unique items)
S5	114256	COMPLEMENT
S6	4	S1 AND S5
S7	3	RD (unique items)
S8	114337	INTERFERON
S9	79	S1 AND S8
S10	285654	GAMMA
S11	74	S9 AND S10

S12 68 S11 NOT S3
S13 1944665 INCREAS?
S14 20 S12 AND S13
S15 12 RD (unique items)
S16 101877 MACROPHAGE
S17 40 S1 AND S16
S18 29 RD (unique items)
S19 1310311 INHIBIT?
S20 13 S18 AND S19
? s activated(5n)macrophage
239693 ACTIVATED
101877 MACROPHAGE
S21 1633 ACTIVATED(5N)MACROPHAGE
? s s1 and s21
833 S1
1633 S21
S22 0 S1 AND S21
?

PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES